



U.S. PHARMACOPEIA
*The Standard of Quality*SM



Biologics in the Compendia – Naming, Definition and Testing Scope: Some Examples

Tina S. Morris, Ph.D.
VP, Biologics & Biotechnology
USP-NF

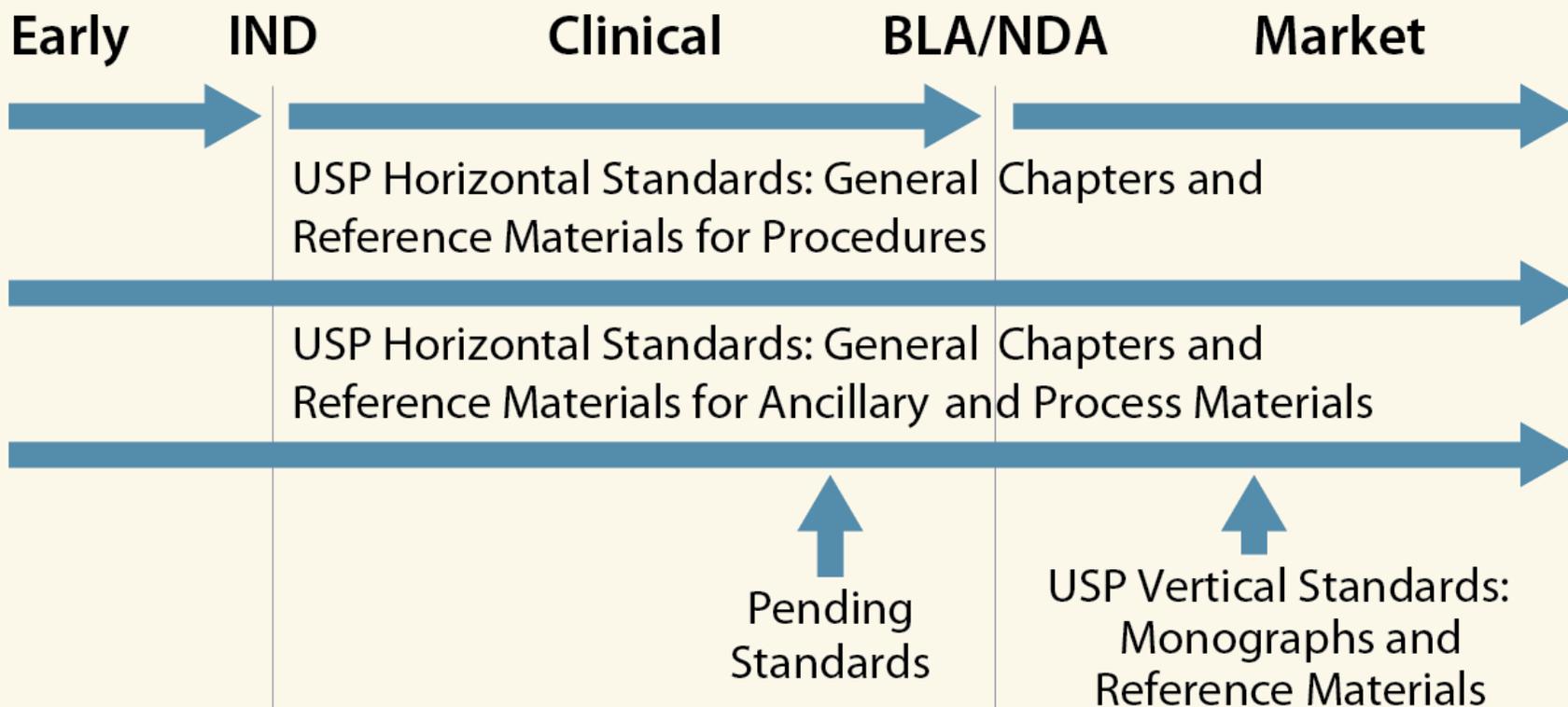
ISO 11238 meeting at USP
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USP Standards – Biologicals

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Application of USP Standards





Recognition of USP Standards in Federal Food Drug and Cosmetic Act (FDCA)

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- **Section 501(b) - Adulterated Drugs and Devices**
 - *A drug or device shall be deemed to be adulterated if it purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium.*
 - *Such determination as to strength, quality, or purity shall be made in accordance with the tests or methods of assay set forth in such compendium...*
- **Section 502(g) Misbranded Drugs and Devices**
 - *A drug or device shall be deemed to be misbranded if it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein.*



Provisions of the FD&C Act apply to biologics regulated under PHS Act

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- PHS ACT (42 USC 262)
 - 262(j) Application of FDCA:
 - *The Federal Food, Drug, and Cosmetic Act... .applies to a biological product subject to regulation under this section, except that a product for which a license has been approved under subsection (a) shall not be required to have an approved application under section 505 of such Act (21 U.S.C. 355)*
- **Biological products approved under the PHS Act are subject to the adulteration and misbranding provisions of FD&C Act**
- **If an official monograph in USP-NF is available, the biological product should conform**



Vertical Standards – Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Role and Use:

- ▶ Clearly define identity, strength and purity, as well as other important quality attributes at the product level
- ▶ Allow independent testing and verification based on a public standard

Considerations for Standard Development:

- ▶ Complexity of specifications and system suitability criteria
- ▶ Biological potency assignments and unit maintenance
 - Across manufacturers
 - Internationally
- ▶ Product- specific vs. common product class requirements
- ▶ For well-characterized and legacy products: inclusion and bridging to new analytical technology



Biological Medicines: Opportunities and Challenges

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ **Biological Medicines: Scope of Products**
 - Blood and Blood Products
 - Cell, Gene, Tissue Therapies
 - Therapeutic Proteins, Recombinant and Naturally-derived
 - Vaccines

- ▶ **Multi-components (e.g. raw materials) manufacturing:**
 - Potential supply chain issues (e.g. animal derived materials)
 - Testing of quality of components before manufacturing begins

- ▶ **Complex manufacturing processes with impact on:**
 - Quality attributes of finished products
 - Challenging regulatory approval pathways

- ▶ **Control of the quality, safety and efficacy of biologicals is difficult, despite technological advances**
 - Orthogonal methods needed to address a single quality aspect
 - Higher order structures, often addressed by a biological assay



Process is the Product Paradigm

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ **The manufacturing process of a biological medicine affects the quality attributes of the product itself**
 - How is this addressed in the context of a compendial standard that accommodates multi-manufacturer products?
 - What defines the product (whether licensed under the PHS Act or FDCA) in terms of identity, strength and purity?



Definition – Key Elements

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ What is the chemical composition?
- ▶ How can it be made?
 - Key process-related requirements may appear here, e.g. viral inactivation, species origin, etc.
- ▶ What activity or activities does it have?
- ▶ Is there a minimal
 - Activity
 - Ratio or content of a moiety or specific chemical group



Definition – Insulin Example

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



$\text{C}_{256}\text{H}_{381}\text{N}_{65}\text{O}_{76}\text{S}_6$ 5777.55
Insulin (pig) [12584-58-6].



$\text{C}_{254}\text{H}_{377}\text{N}_{65}\text{O}_{75}\text{S}_6$ 5733.50
Insulin (ox) [11070-73-8].

» Insulin is a protein that affects the metabolism of glucose. It is obtained from the pancreas of healthy bovine or porcine animals, or both, used for food by humans. Its potency, calculated on the dried basis, is not less than 26.5 USP Insulin Units in each mg; Insulin labeled as purified contains not less than 27.0 USP Insulin Units in each mg, calculated on the dried basis. The proinsulin content, determined by a validated method, is not more than 10 ppm.

NOTE—One USP Insulin Unit is equivalent to 0.0342 mg of pure Insulin derived from beef or 0.0345 mg of pure Insulin derived from pork.



Questions of Identity

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

From *USP General Notices PF 36(1)*:

A compendial test titled Identity or Identification is provided to establish the identity of an article as it is purported to be, i.e., whether it is the article named in USP-NF. The Identity or Identification test for a particular article may consist of one or more procedures. When a compendial test for Identity or Identification is undertaken, all requirements of all specified procedures in the test must be met to satisfy the requirements of the test. Failure of an article to meet all the requirements of a prescribed Identity or Identification test (i.e. failure to meet the requirements of all of the specified procedures that are components of that test) indicates that the article is mislabeled and/or adulterated.



Elements of Identification for Biological Products

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Orthogonality
 - More than one test should be used to demonstrate identity, each test should measure a different attribute of the molecule
- ▶ Specificity – see USP <1225> *Validation of Compendial Procedures* and ICHQ2R1
 - Identification Tests require the demonstration of specificity as the primary goal in validation
- ▶ Activity/function
 - May be called out separately as *Bioidentity*
 - May also be part of the Definition



Identification – Example 1: Insulin Human

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Identification—

- ▶ A: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the

Assay.

- ▶ B: Determine the peptide fragments, using the following peptide mapping procedure.

Identification and other Tests are often linked



Production System Differences

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Calcitonin Salmon is a polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. **It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology.** The host cell-derived protein content and the host cell- or vector-derived DNA content of Calcitonin Salmon produced from an rDNA process are determined by validated methods. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid-free and dried basis.



In *Calcitonin Salmon*:

Identification – The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that of the Standard preparation, obtained as directed in the Assay.

Amino acid profile (see Biotechnology-Derived Articles – Amino Acid Analysis 1052)

[NOTE—This test needs to be performed only on material of synthetic origin.]



In *Calcitonin Salmon*:

Related peptides and other related substances—

TEST 1—[NOTE—This test is performed on material produced by both chemical and recombinant DNA processes.]



Complexity as a Challenge

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

▶ Complexity derived from

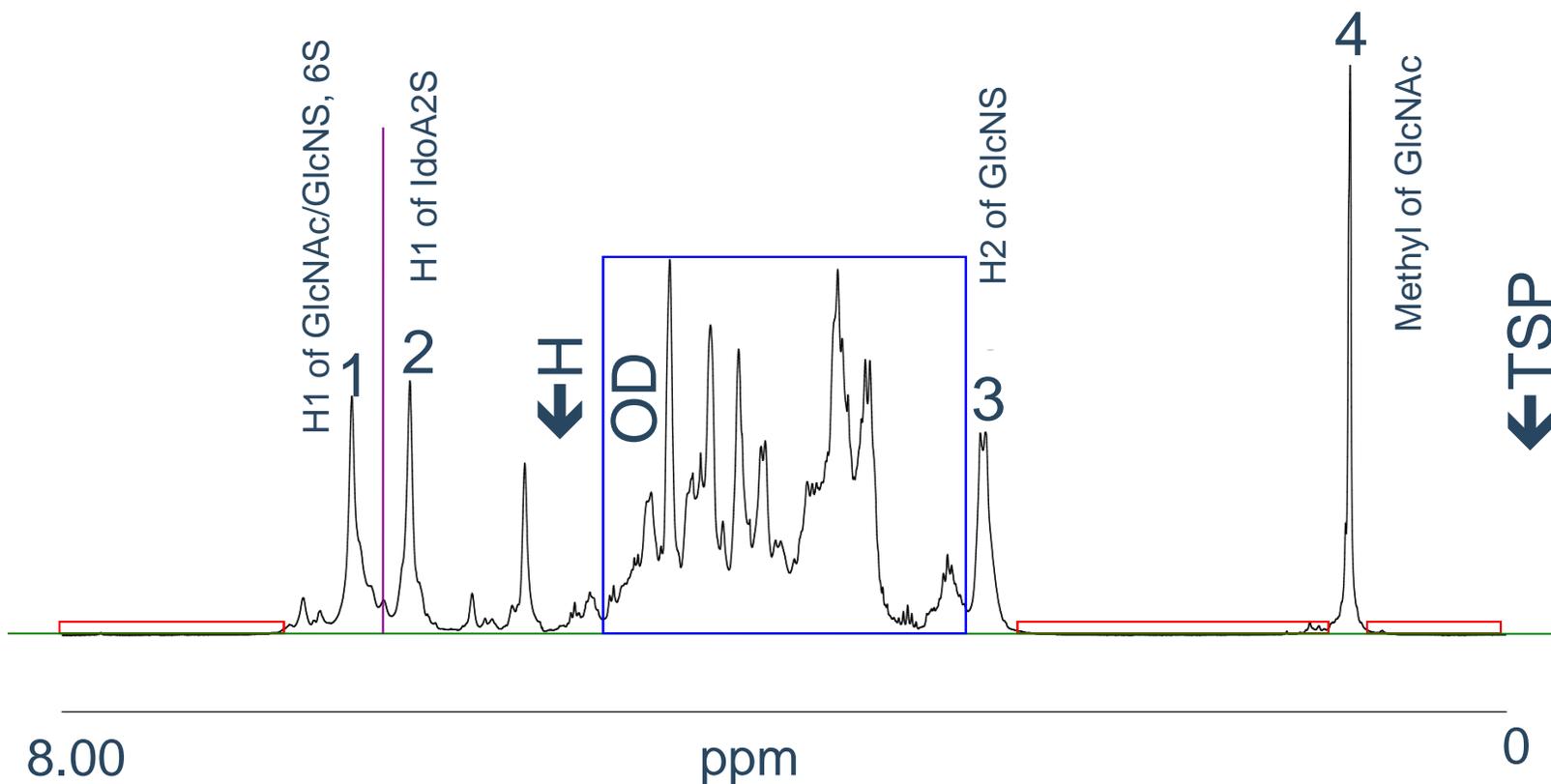
- Molecular heterogeneity: e.g. polydispersity
- Manufacturing or process differences
- Differences in natural sources
poses a considerable challenge to applying platform
and class approaches.

Can this be addressed?



^1H NMR Specification for Identity of Heparin

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Acceptance Criteria

- No unidentified signals greater than 4% of the mean of signal height of 1 and 2 are present in the following ranges: 0.10-2.00, 2.10-3.20, and 5.70-8.00 ppm.
- No signals greater than 200% signal height of the mean of the signal height of 1 and 2 are present in the 3.35-4.55 ppm for porcine heparin.



Product Type versus Molecule Class – Platform Accessibility

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

Product Type	Molecule Class	Source	Legacy Products in this Class?	Accessible to platform approach?
Cell Therapy	Whole Cell	Patient-autologous	No	No
Clotting Factor	Protein/Enzyme	Plasma and recombinant	Yes	to some extent
Cytokine or growth factor	Peptide or small protein	Mostly recombinant	Yes - hormones	Yes
Enzyme	Protein	Both recombinant and naturally derived	Yes	Yes
Monoclonal antibody	Protein, IgG1	Recombinant	No	Yes
Polyclonal antibody	Protein, Ig mixture	Plasma-derived	Yes	to some extent
Toxin	Protein	Both recombinant and naturally derived	Yes	Yes
Vaccine	Various	Both recombinant and naturally derived	Yes	to some extent
Other – what about heparin?	Polydisperse glycosaminoglycan	Naturally derived	Yes	Yes



Peptide/Small Protein Drug Substance Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

	Somatropin	Insulin Human	Glucagon	Filgrastim
Identification - HPLC	X	X	X	X
Identification - Peptide Mapping	X	X	X	X
Assay - HPLC	X	X	X	
Impurities – related proteins: HPLC (Assay)	X	X	X	X
Impurities – Charge variants, IEF				X
Impurities – Limit of HMW proteins: SEC	X	X		X
Specific Tests: bioidentity, <85>, <61>/<62>, <731>	X	X	no bioidentity test for DS	no <731>



Filgrastim Drug Substance Monograph

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Definition:
 - “It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escheria coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains NLT 1.0 mg/mL of Filgrastim. . . . It has a biological potency of NLT 80% and NMT 125% relative to the standard.”

- ▶ Identity

- ▶ Assay (Potency)

- ▶ Impurities

- ▶ Additional Requirements
 - Packaging and Storage; Labeling

- ▶ Reference Standards



Filgrastim Monograph: *Identification*

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ A. It meets the requirements described under Assay.
 - Acceptance criteria: It has a biological potency of NLT 80% and NMT 125%.

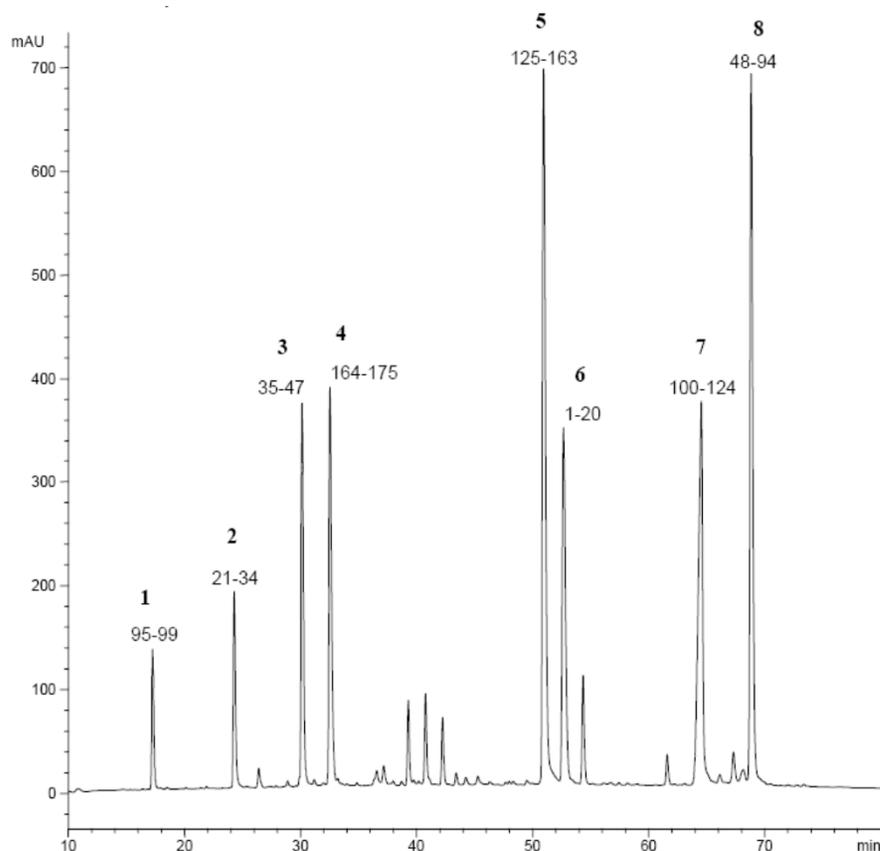
- ▶ B. It meets the requirements described under *Chromatographic purity*.
 - Acceptance criteria: NMT 1.0% of reduced Filgrastim is found and NMT 2.0% of total impurity is found.

- ▶ C. Peptide mapping with UV detection
 - Acceptance criteria: next slide



Identification C: Peptide Mapping with UV Detection

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients



Acceptance criteria: The difference in retention of each of the eight major peaks between the *Test solution* chromatogram and the average of the *Standard solution* chromatograms must be ≤ 0.5 min. The relative difference in peak height between the normalized sample peak height (normalized by total peak height versus the average total peak height of the *Standard solution* chromatograms) and the average standard peak height of each of the eight major peaks must be $\leq 15\%$.

NOTE: 8 major peaks will be defined in the USP Filgrastim RS Data Sheet.



Pancreatin – Drug Substance Monograph

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

▶ Definition:

Pancreatin is a substance containing enzymes, principally amylase, lipase, and protease, obtained from the pancreas of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. Suidae) or of the ox, *Bos taurus* Linné (Fam. Bovidae). Pancreatin contains, in each mg, not less than 25 USP Units of amylase activity, not less than 2.0 USP Units of lipase activity, and not less than 25 USP Units of protease activity.

▶ Enzymatic Assays

- Amylase, Lipase, Protease

▶ Fat Content Test

▶ General Requirements: Labeling, Packaging and Storage

▶ Identification will be addressed in revision

- Products must meet enzymatic assays (e.g. Lipase assay)
- Inclusion of identification test (HPLC-based)



Assay – Amount of Substance or Activity?

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

ICH Q6B:

2.1.2 Biological activity

Assessment of the biological properties constitutes an equally essential step in establishing a complete characterization profile. An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect.

Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product which is linked to the relevant biological properties, whereas, quantity (expressed in mass) is a physicochemical measure of protein content. Mimicking the biological activity in the clinical situation is not always necessary. A correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.



USP General Notices:

5.50.10. Units of Potency (Biological)

For substances that cannot be completely characterized by chemical and physical means, it may be necessary to express quantities of activity in biological units of potency, each defined by an authoritative, designated reference standard.

Units of biological potency defined by the World Health Organization (WHO) for International Biological Standards and International Biological Reference Preparations are termed International Units (IU). Monographs refer to the units defined by USP Reference Standards as “USP Units.” For biological products, units of potency are defined by the corresponding U.S. Standard established by FDA, whether or not International Units or USP Units have been defined



Insulin Human:

NOTE—One USP Insulin Human Unit is equivalent to 0.0347 mg of pure Insulin Human.

Insulin:

NOTE—One USP Insulin Unit is equivalent to 0.0342 mg of pure Insulin derived from beef or 0.0345 mg of pure Insulin derived from pork.

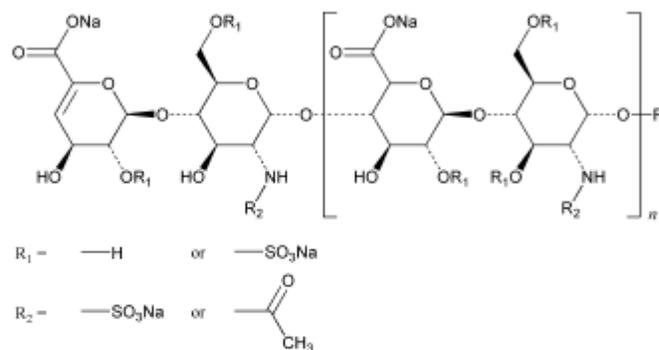
The Bioassay (rabbit blood glucose test) is used for *Bioidentity* only.



The Use of IU in USP Monographs

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

■ Enoxaparin Sodium



$R =$	$X = 15 - 25\%$		$n = 0 \text{ to } 20$
	$100 - X$	H	$n = 1 \text{ to } 21$

[9041-08-1].

1.8 per disaccharide unit. It has a potency of not less than 90 and not more than 125 Anti-Factor X_a International Units (IU) per mg, and not less than 20.0 and not more than 35.0 Anti-Factor II_a IU per mg, calculated on



Mass/Activity Correlation – A More Complicated Example

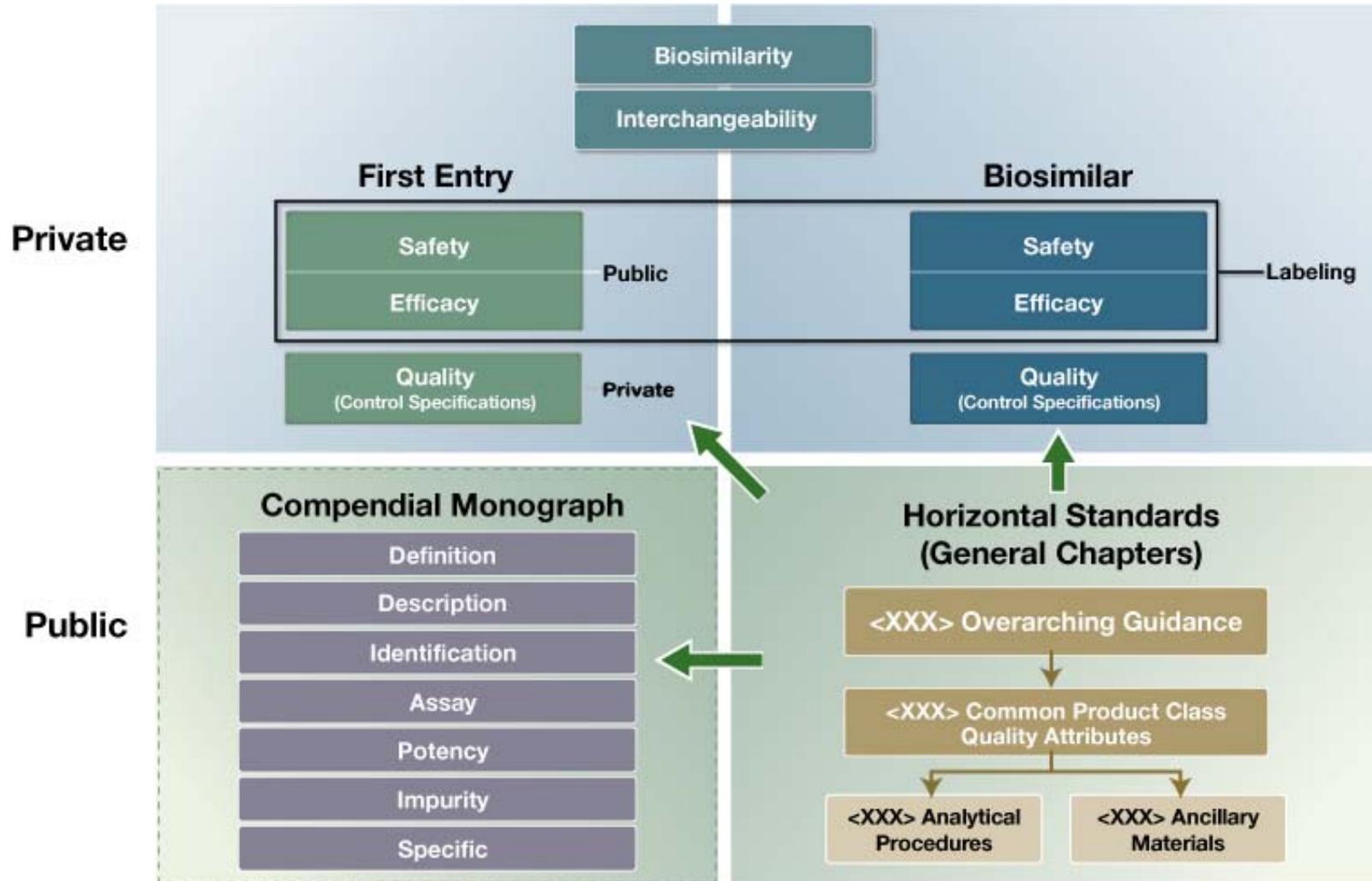
Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

- ▶ Pancrelipase is a substance containing enzymes, principally lipase, with amylase and protease, obtained from the pancreas of the hog, *Sus scrofa* Linné var. *domesticus* Gray (Fam. Suidae). It contains, in each mg, not less than 24 USP Units of lipase activity, not less than 100 USP Units of amylase activity, and not less than 100 USP Units of protease activity.



Biologics Standards

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients





Thank You!

Quality Standards for Medicines, Dietary Supplements, and Food Ingredients

